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Datasheet for the decision of 30 September 2021

Case Number: T 0500/16 - 3.3.02

Application Number: 10701175.1

Publication Number: 2387563

IPC: C07D215/227, A61K31/47, A61P35/00

Language of the proceedings: EN

Title of invention:

MALATE SALT OF N- (4- { [6, 7-BIS (METHYLOXY) QUINOLIN-4-YL]OXY}PHENYL-N' - (4 -FLUOROPHENYL) CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEREOF FOR THE TREATMENT OF CANCER

Patent Proprietor:

Exelixis, Inc.

Opponents:

Gallafent, Alison
Actavis Group PTC ehf
Ladendorf, Oliver

Headword:

Relevant legal provisions:

EPC Art. 56, 54, 83
RPBA Art. 12(4), 13(1), 13(3)
RPBA 2020 Art. 12(2), 25(2)

Keyword:

Inventive step
Novelty
Sufficiency of disclosure
Late-filed facts

Decisions cited:

G 0003/14, T 0184/00, T 1329/04, T 0710/05, T 0608/07, T 0777/08, T 0415/11, T 1744/14, T 1875/15, T 0184/16, T 0488/16, T 1083/16, T 1684/16, T 0405/17

Catchword:

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Beschwerdekammern

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Case Number: T 0500/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 30 September 2021

Appellant: (Opponent 1)	Gallafent, Alison Alison Gallafent Ltd 21 Bridge St Llandeilo SA19 6BN (GB)
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Respondent: (Patent Proprietor)	Exelixis, Inc. 210 East Grand Avenue P.O. Box 511 South San Francisco, CA 94080-0511 (US)

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 January 2016 concerning maintenance of the European Patent No. 2387563 in amended form.**

Composition of the Board:

Chairman M. O. Müller
Members: S. Bertrand
M. Blasi

Summary of Facts and Submissions

I. The appeals by the opponents lie from the interlocutory decision of the opposition division that European patent No. 2 387 563 in amended form according to the main request comprising the set of claims filed on 22 September 2014 met the requirements of the EPC.

II. The main request contains a set of fourteen claims, independent claim 1 of which reads as follows:

"1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is crystalline."

III. The following documents are referred to in the present decision:

D3 J. K. Guillory, Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids; Polymorphism in Pharmaceutical Solids, Brittain (ed.), 1990, pp. 183-226

D5 L. Kumar *et al.*, Preparation and Characterization of Salt Forms of Enalapril, Pharmaceutical Development and Technology, 2008, volume 13, pp. 345-357

D7 L. Kumar *et al.*, An overview of automated systems relevant in pharmaceutical salt screening, Drug discovery Today, 2007, volume 12, pp. 1046-1053

D10 S.M. Berge *et al.*, Pharmaceutical Salts, Journal of Pharmaceutical Sciences, 1977, volume 66, pp. 1-19

D13 W.Q. Tong, Salt Screening and Selection: New Challenges and Considerations in the Modern Pharmaceutical R&D Paradigm, Integrated Drug Product Development Process (three day course), 2006

D14 A.R. Gennaro, Remington: The Science and Practice of Pharmacy, 20th edition, 2000, pp. 712-713

D25 S. Byrn *et al.*, Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations, Pharmaceutical Research, 1995, volume 12, pp. 945-954

D26 M. Bavin, Polymorphism in Process Development, Chemistry & Industry, 1989, pp. 527-529

D29 EMEA; Committee for Orphan Medicinal Products; December 2008, Plenary Meeting Monthly Report

Annex 1 Experimental evidence submitted by the patent proprietor with the reply to the notice of opposition

D32 Experimental evidence provided by Sandoz GmbH on 14 November 2015

D33 Declaration of Prof Dr Ulrich Griesser

D35 J. Meulenaar *et al.*, Slow dissolution behaviour of amorphous capecitabine, International Journal of Pharmaceutics, 2013, pp. 213-217

A001 Pharmaceutics: The Science of Dosage Form Design, Aulton (ed.), 2002, pp. 7-8

A002 IUPAC-definitions of "solubility", 2014

A003 IUPAC-definitions of "dissolution", 2014

A004 O. Akutsu *et al.*, An X-Ray Diffraction System with Controlled Relative Humidity and Temperature, The Rigaku Journal, 1997, volume 14, pp. 1-4

A005 B.C. Hancock *et al.*, Molecular Mobility of Amorphous Pharmaceutical Solids Below Their Glass Transition Temperatures, Pharmaceutical Research, 1995, volume 12, pp. 799-806

A006 C.S. Towler *et al.*, An Investigation into the Influence of Couterion on the Properties of Some Amorphous Organic Salts, Molecular Pharmaceutics, 2008, volume 5, pp. 946-955

A007 TEVA experiment, reproduction of example 2 of the patent, 2016

IV. In the impugned decision, the opposition division's conclusions included the following.

- The claims according to the main request fulfilled the requirements of Article 123(2) and (3) EPC.
- The invention as defined in the main request was sufficiently disclosed within the meaning of Article 83 EPC.
- The subject-matter of the claims according to the main request was novel pursuant to Article 54 EPC.
- The subject-matter of the claims according to the main request involved an inventive step in view of D29 as the closest prior art (Article 56 EPC).

V. In the statement setting out the grounds of appeal, opponent 1 ("appellant 1") contested the reasoning of the opposition division and submitted that the invention defined in the claims according to the main request was not sufficiently disclosed and that the subject-matter of the claims of this request did not involve an inventive step. It submitted documents A001 to A005 (denoted D36 to D40 by appellant 1).

VI. In the statement setting out the grounds of appeal, opponent 2 ("appellant 2") submitted that the subject-matter of the claims according to the main request was not novel and did not involve an inventive step.

VII. In the statement setting out the grounds of appeal, opponent 3 ("appellant 3") submitted that the invention defined in the claims according to the main request was not sufficiently disclosed and that the subject-matter of the claims of this request contained added subject-matter, was not novel and did not involve an inventive step. It submitted document A006 (denoted D36 by appellant 3).

VIII. In its reply to the grounds of appeal, the patent proprietor ("respondent") provided counter-arguments on added subject-matter, sufficiency of disclosure, novelty and inventive step. It submitted sets of claims of auxiliary requests 1 to 25.

IX. In a further letter, appellant 2 submitted document A007 (denoted D42 by appellant 2) and further arguments on insufficiency of disclosure based on this document.

X. In a second further letter, appellant 2 submitted further arguments on lack of novelty and inventive step and commented on the auxiliary requests.

XI. In a letter in reply to the submissions filed by the respondent, appellant 3 submitted further arguments on added subject-matter and lack of novelty and inventive step, also in relation to the auxiliary requests.

XII. In a further letter, the respondent submitted arguments on added subject-matter, sufficiency of disclosure, novelty and inventive step in response to the appellants' submissions.

XIII. On 7 August 2020, the board issued a communication in preparation for the oral proceedings, which were to be arranged as requested by the parties.

XIV. Appellant 2 filed further submissions on inventive step with a third further letter. It also withdrew the request that A007 and the associated objection of lack of sufficiency of disclosure be admitted into the proceedings.

XV. In a second further letter, the respondent requested that some of the objections of lack of sufficiency of disclosure raised by appellants 1 and 3 not be admitted. It further requested that the submissions made by appellants 1 and 2 based on plausibility and bonus effect not be admitted.

XVI. Oral proceedings before the board were held on 30 September 2021 by videoconference.

XVII. Appellant 1's arguments, where relevant to the present decision, may be summarised as follows.

Sufficiency of disclosure

- The application as filed did not disclose in a manner sufficiently clear and complete how to obtain all the embodiments covered by claim 1 of the main request.

- Relative humidity and temperature were important factors that should be controlled when measuring an X-ray powder diffraction XRPD, as shown by A004. Since these factors were not defined in claims 6 and 8, this amounted to an undue burden on the skilled person to select the adequate conditions for measuring the XRPD of the compound of claim 6 or 8.

- Because of a discrepancy between claims 6 and 7 of the main request and between claims 8 and 9 of the main request, the skilled person was unable to unambiguously determine whether they were operating within the scope of claims 6 and 8 of the main request. Thus, the invention underlying the subject-matter of claim 6 or 8 was not sufficiently disclosed.

Inventive step

- D29 was the closest prior art.

- The distinguishing feature of the subject-matter of claim 1 of the main request over the disclosure of D29 was the crystalline form of the cabozantinib malate salt.

- The results in annex 1 were only a bonus effect since the skilled person would have had ample motivation in view of the teachings of D3 and D5 to select the crystalline form of the cabozantinib malate salt disclosed in D29.

- Annex 1 was not suitable for demonstrating an inventive step over D29. Comparative data had been provided for only one crystalline form of the cabozantinib malate salt, and it could not be concluded that the effect was achieved across the whole scope of claim 1 of the main request. Furthermore, the comparison did not represent a true comparison with the compound of D29 since the compared composition was a mixture of a crystalline and an amorphous form. The true comparison should have been made with amorphous cabozantinib (L)-

malate alone. Furthermore, annex 1 only showed an "excipient effect".

- The objective technical problem was the provision of a form of the cabozantinib malate salt suitable for use in a pharmaceutical composition.

- D3, D7, D13, D14, D25, D26, A005 and A006 showed that it was routine practice to screen crystalline forms of a drug. The skilled person would have arrived at the subject-matter of claim 1 of the main request without inventive merit.

- This conclusion was in accordance with T 777/08.

XVIII. Appellant 2's arguments, where relevant to the present decision, may be summarised as follows.

Novelty

- D29 implicitly disclosed the crystalline and amorphous forms of the cabozantinib malate salt and thus anticipated the crystalline form as claimed.

Inventive step

- D29 was the closest prior art.

- The distinguishing feature of the subject-matter of claim 1 of the main request over the disclosure of D29, if any, was the crystalline form of the cabozantinib malate salt.

- The effect relied on in annex 1 was not made plausible in the application as filed. Post-

published annex 1 should not be considered in the formulation of the objective technical problem.

- If annex 1 were to be considered, its data would not be relevant. The comparative examples used in annex 1 fell within the scope of claim 1 of the main request since the claim did not require any limitation of the content of the crystalline form.

- If it were considered that the comparative example of annex 1 did not fall within the scope of claim 1 of the main request, annex 1 would only show an "excipient effect".

- If annex 1 were to be considered, the effect would be a bonus effect, with the prior art teaching to prefer the crystalline form of a drug.

- Considering D29 as the closest prior art and in view of the bonus effect shown in annex 1, the objective technical problem was the provision of a particular form of the cabozantinib malate salt.

- D25 and D26 rendered the solution proposed by claim 1 of the main request obvious.

Admittance of the submissions based on plausibility

- Admittance of respondent's request for non-admittance of appellant 2's submissions on a lack of plausibility

  - The respondent's request for non-admittance of appellant 2's submissions on a lack of plausibility was submitted with the letter of 20 October 2020, i.e. after the issuance of the

summons to attend oral proceedings. It was not submitted in the reply to the grounds of appeal.

- The respondent's request should not be admitted into the proceedings.

- Admittance of the objection of lack of plausibility

  - The objection of lack of plausibility did not constitute an allegation of fact. It was only an argument.

  - The objection of lack of plausibility could only have been raised with the statement of grounds of appeal since the case law on plausibility cases involving "small" molecules was only developed after the proceedings before the opposition division.

  - The objection should be admitted into the proceedings.

XIX. Appellant 3's arguments, where relevant to the present decision, may be summarised as follows.

Sufficiency of disclosure

- The application as filed did not contain a single example of a pharmaceutical composition comprising a cabozantinib malate salt and a pharmaceutically acceptable excipient. This represented a lack of sufficiency of disclosure of the pharmaceutical composition of claim 10.

Novelty

- D29 implicitly disclosed the crystalline and amorphous forms of the cabozantinib malate salt and thus anticipated the crystalline form as claimed.

Inventive step

- D29 was the closest prior art.

- The distinguishing feature of the subject-matter of claim 1 of the main request over the disclosure of D29, if any, was the crystalline form of the cabozantinib malate salt.

- The comparison in annex 1 was not suitable since it did not differ only by the distinguishing feature. The compared composition was a mixture of a crystalline form and an amorphous form and not a composition comprising only the amorphous form. Furthermore, the effect shown in annex 1 was an excipient effect.

- The amorphous form of the cabozantinib malate salt had a solubility higher than the crystalline form, as shown by D32 and D33 and expected in the art.

- In view of D32, the objective technical problem could only be seen as the provision of a specific solid form of the cabozantinib malate salt.

- Starting from D29 as the closest prior art, the provision of the crystalline form of the cabozantinib malate salt was one of only two alternatives, and the selection of one among only two alternatives was not based on an inventive

step. The selection of the crystalline form of the cabozantinib malate salt disclosed in D29 was according to the teaching of D25.

- Thus, the subject-matter of claim 1 did not involve an inventive step. This conclusion was in line with T 777/08.

XX. The respondent's arguments, where relevant to the present decision, may be summarised as follows.

Admittance of the objection of added subject-matter

- The objection should not be admitted into the proceedings.

- In the summons to oral proceedings, the opposition division gave the preliminary view that the provisions of Article 123(2) EPC appeared to be met.

- During the proceedings before the opposition division, no objection under Article 123(2) EPC was raised by the appellants.

- The objection could and should have been submitted during the proceedings before the opposition division.

Sufficiency of disclosure

- Salts of claim 1 of the main request

  - The application as filed provided enough guidance to enable the skilled person to obtain compounds according to the invention. There were

no serious reasons to doubt that the skilled person could prepare the claimed compounds.

- XRPD of claims 6 and 8 of the main request

  - These claims referred to a measurement made at room temperature, so appellant 1's allegation concerning the missing temperature for the XRPD measurement was unjustified.

  - Appellant 1 provided no evidence that moisture uptake by the crystalline form of the cabozantinib malate salt would alter the XRPD measurement.

- Salts encompassed by claims 6 to 9

  - The objection should not be admitted into the proceedings since the objection was not raised before the opposition division.

  - Appellant 1's objection was an allegation that the claims lacked clarity. Since the lack of clarity was present in the granted claims, appellant 1's submission in this regard could not succeed.

- Pharmaceutical composition of claim 10 of the main request

  - The objection should not be admitted into the proceedings since the objection was not raised before the opposition division.

  - Paragraphs [0065] and [0077] to [0086] of the application as filed provided the required

information for the skilled person to prepare the pharmaceutical composition of claim 10 of the main request.

Novelty

- D29 (page 1) disclosed cabozantinib (L)-malate for treatment of medullary thyroid carcinoma, but it could not be deduced from the disclosure that the salt was crystalline. The subject-matter of claim 1 of the main request, requiring a crystalline form, was thus novel.

Inventive step

- D29 was the closest prior art.

- The distinguishing feature of the subject-matter of claim 1 of the main request over the disclosure of D29 was the crystalline form of the cabozantinib malate salt.

- The results of annex 1 showed that the dissolution profile of tablets and capsules comprising 100% crystalline cabozantinib (L)-malate was improved in an acidic medium at 37°C in comparison to the same tablets and capsules in which the crystalline form was partially replaced by the amorphous form.

- The objective technical problem was the provision of a cabozantinib malate salt which, as a pharmaceutical formulation, has an improved dissolution profile under physiological conditions.

- The skilled person would not have been directed to any crystalline form of the cabozantinib malate

salt, with the prior art teaching that amorphous forms of drugs are usually more soluble than their crystalline counterparts. Reference was made to D3, D5, D7, D13, D14, D25, D35, A005 and A006.

- The effect shown by annex 1 was not expected, so the case at hand was not in contradiction with T 777/08.

- The appellants' submissions on inventive step were not correct.

  - The effect shown by annex 1 was not a bonus effect since there was no one-way street situation in the case at issue. Reference was made to D3, D5, D7, D13, D14, D25, D35, A005 and A006, which showed that the skilled person would not have selected the crystalline form of the cabozantinib malate salt to solve the objective technical problem.

  - Annex 1 was a fair comparison with D29. There was no reason to assume that the comparative examples of annex 1 could not be representative of a composition comprising 100% of the amorphous form.

  - It could not be concluded from the data in annex 1 that there was only an excipient effect. The burden of proof was on the appellants to show that the excipients interacted differently with the amorphous form when compared to the crystalline form of cabozantinib (L)-malate.

  - Document D32 did not relate to the same property as that shown in annex 1, as evidenced by D10.

Furthermore, the experiments in D32 were not carried out at the same temperature and under the same acidic conditions as those of annex 1.

- The effect shown in annex 1 was credibly achieved over the whole scope of claim 1 of the main request. The burden of proof for the allegation that the improvement was not achieved over the whole scope of the claim was on the appellants.

Admittance of the submissions based on plausibility

- Admittance of the respondent's request for non-admittance of appellant 2's submissions on a lack of plausibility

  - The respondent's request for non-admittance of appellant 2's submissions on a lack of plausibility was raised with the letter of 20 October 2020, i.e. almost one year before the oral proceedings. It was not submitted at an extremely late stage of the appeal proceedings.

  - The respondent's request did not raise any complex new issue. The submissions met the requirements of Article 13(1) and (3) RPBA 2020.

- Admittance of the objection of lack of plausibility

  - The objection was made for the first time in the statement of grounds of appeal. The objection could and should have been presented in the proceedings before the opposition division.

  - The submission was an allegation of fact since it was linked to the surprising property of an

improved dissolution profile to be taken into account or not for formulating the objective technical problem.

- The concept of plausibility of small molecules was known in the case law in 2007 as evidenced by T 710/05. This case law was thus available during the opposition proceedings, and the objection on lack of plausibility should have been filed then.

- The objection should not be admitted under Article 12(4) RPBA 2007.

- Furthermore, admitting the objection into the proceedings would give appellant 2 a second chance to object to inventive step based on an entirely new submission, subsequent to the termination of the opposition proceedings, contrary to the requirement of Article 12(2) RPBA 2020.

Admittance of the allegation of fact based on a bonus effect

- The allegation of fact based on a bonus effect could and should have been presented in the proceedings before the opposition division. It should not be admitted into the proceedings under Article 12(4) RPBA 2007.

Admittance of the submissions on the particle size used in annex 1 and the use of film-coated tablets

- These submissions were made for the first time during the oral proceedings, at a very late stage of the proceedings. The submissions raised complex

new technical issues and should not be admitted into the proceedings pursuant to Article 13(1) and (3) RPBA 2007.

XXI. The parties' final requests were as follows.

Appellant 1 requested that:

- the decision under appeal be set aside and that the patent be revoked in its entirety

- documents A001-A005 be admitted into the proceedings

Appellant 2 requested that:

- the decision under appeal be set aside and that the patent be revoked in its entirety

- the respondent's requests for non-admittance of the appellants' submissions on plausibility and bonus effect not be admitted into the proceedings

Appellant 3 requested that:

- the decision under appeal be set aside and that the patent be revoked in its entirety

- document A006 be admitted into the proceedings

- the respondent's requests for non-admittance of the submissions on plausibility and bonus effect not be admitted into the proceedings

The respondent requested that:

- the appeal be dismissed, implying that the main request held allowable by the opposition division be upheld

- alternatively, the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 25 filed with the reply to the statements of grounds of appeal

- the objection of added subject-matter not be admitted into the proceedings

- the objection of lack of plausibility and the related objection that post-published evidence annex 1 not be taken into account not be admitted into the proceedings

- the allegation of fact based on a bonus effect not be admitted into the proceedings

- the objections of lack of sufficiency of disclosure in view of (i) a discrepancy between claims 6 (100% N1) and 7 (>90% N1) and between claims 8 (100% N2) and 9 (>90% N2) and (ii) the amount and nature of the pharmaceutically acceptable excipient of claim 10 not be admitted into the proceedings

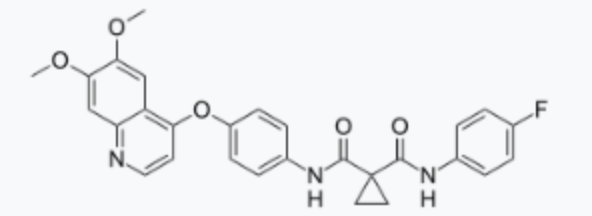
Reasons for the Decision

Main request

1. Claim 1 of the main request relates to "*N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is crystalline*".

   N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide is referred to in the following as cabozantinib.

   Cabozantinib has the following chemical formula:



2. Admittance of the objections of added subject-matter under Article 12(4) RPBA 2007

2.1 In its statement of grounds of appeal, appellant 3 submitted that the feature "wherein said salt is crystalline" in claim 1 of the main request was not based on the application as filed. Appellant 3 also submitted that the application as filed did not contain any direct and unambiguous disclosure on mixtures of the (D)-malate salt and the (L)-malate salt in any conceivable molar ratios in which both the (D)-malate salt and the (L)-malate would be crystalline. Such

mixtures were encompassed by claim 1 of the main request.

2.2 The respondent requested that the appellant's objections not be admitted into the proceedings.

2.3 Appellant 3 raised the objections of added subject-matter against claim 1 of the main request for the first time in the statement of grounds of appeal.

Pursuant to Article 12(4) RPBA 2007, which applies to the case at hand in accordance with the transitional provisions set out in Article 25(2) RPBA 2020 (the statement of grounds of appeal having been filed before 1 January 2020), the board has the power to hold inadmissible, *inter alia*, facts and evidence which could have been presented in the first-instance proceedings even if they were presented with the statement of grounds of appeal and meet the requirements of Article 12(2) RPBA 2007.

In this case, the objection at issue could and should have been filed during the proceedings before the opposition division for the following reasons.

The set of claims of the current main request was submitted with the reply to the notice of opposition. Article 123(2) EPC was addressed in the communication accompanying the summons of 12 June 2015 by the opposition division (point 7). In this communication, the opposition division mentioned the basis in the application as filed for claim 1 of the main request and gave the preliminary view that the provisions of Article 123(2) EPC appeared to be met. Appellant 3, in the reply to the opposition division's communication, only raised an objection under Article 123(3) EPC (point 5 of the letter) but did not raise any objection

under Article 123(2) EPC. In section 4.1 of its decision, the opposition division dealt with Article 123(2) and (3) EPC. The only objection from appellant 3 mentioned in this section was the objection under Article 123(3) EPC. In fact, the minutes of the opposition division referred to a discussion on Article 123(3) EPC but not on Article 123(2) EPC (point 2 of the minutes). Consequently, the issue regarding added subject-matter in claim 1 of the main request was not addressed by appellant 3 during the proceedings before the opposition division, even though it had several opportunities to do so. In fact, appellant 3 did not make any submission on why the objection was only raised with the statement of grounds of appeal. Appellant 3 thus could and should have raised this objection before the opposition division.

Thus, the board decided not to admit the objection into the proceedings in accordance with Article 12(4) RPBA 2007.

3. Sufficiency of disclosure - Article 83 EPC

Appellants 1 and 3 objected to the sufficiency of disclosure of the subject-matter of claims 1 and 6 to 10 of the main request.

3.1 Salts of claim 1 of the main request

3.1.1 As set out above, claim 1 of the main request refers to a cabozantinib malate salt which is crystalline.

3.1.2 Appellant 1 submitted that the application as filed did not disclose in a manner sufficiently clear and complete how to obtain all the embodiments covered by claim 1 of the main request. Claim 1 of the main request covered any polymorphic states of the

cabozantinib malate salt, any ratios of cabozantinib to malic acid and any salts of all stereoisomers of malic acid.

3.1.3 The board is of the view that the application as filed discloses the invention defined in claim 1 of the main request in a manner sufficiently clear and complete for it to be carried out for the following reasons.

The fact that claim 1 of the main request covers various polymorphic states, ratios and stereoisomers cannot alone give rise to insufficiency of disclosure. In the absence of serious reasons substantiated by verifiable facts to doubt that the skilled person can prepare the claimed compounds in these polymorphic states and ratios and with these stereoisomers, appellant 1's objection cannot succeed.

3.2 XRPD of claims 6 and 8 of the main request

As set out above, claims 6 and 8 of the main request relate to crystalline forms N-1 and N-2 of a cabozantinib malate salt. These are characterised in these claims by various alternative characteristics, including an XRPD with specified 2θ values or an XRPD substantially in accordance with the pattern of Figure 1 or 2.

Appellant 1 essentially submitted that relative humidity and temperature were important factors that should be controlled when measuring an XRPD, as shown by A004. It also referred to Figures 7, 14 and 21 of the patent, which showed the moisture sorption of forms N-1 and N-2.

In the board's view, the invention defined in claims 6 and 8 of the main request with regard to XRPD

characteristics is sufficiently disclosed for the following reasons.

Firstly, as submitted by the respondent, these claims specify that the measurement of the XRPD characteristics has to be made at room temperature ("*wherein measurement of the crystalline form is at room temperature*"). Therefore, appellant 1's submissions regarding the temperature must fail.

Secondly, with regard to the relative humidity, an objection of lack of sufficient disclosure, in order to succeed, presupposes that there are serious doubts, substantiated by verifiable facts, that the application or patent, respectively, discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. To establish insufficiency, the burden of proof is upon the opponent to demonstrate that the skilled person, using common general knowledge, would be unable to carry out the invention (see decision T 1744/14, reasons, 2.2). In the case at issue, appellant 1 provided no data showing that the XRPD of the cabozantinib malate salt of claim 6 or 8 of the main request depends on the relative humidity. The reference to A004 is not relevant. A004 reports on the influence of humidity and temperature on the XRPD of hygroscopic minerals (montmorillonite and sodium chloride). However, it does not establish that a different compound, namely the cabozantinib malate salt of claims 6 and 8 according to the main request, is hygroscopic and, thus, that the relative humidity would alter the measurement of the XRPD of this salt. In the absence of verifiable facts, appellant 1's argument does not establish insufficiency of disclosure of the invention defined in claims 6 and 8 of the main request.

3.3 Salts encompassed by claims 6 to 9 of the main request

Appellant 1 submitted that because of a discrepancy between claims 6 and 7 of the main request and between claims 8 and 9 of the main request, the skilled person was unable to determine unambiguously whether they were operating within the scope of claims 6 and 8 of the main request. Thus, the claimed invention was not sufficiently disclosed in the application.

Claims 6 and 8 relate to crystalline forms N-1 and N-2 of a cabozantinib malate salt. The board acknowledges that this means that the cabozantinib malate salts of claims 6 and 8 are (about) 100 wt.% N-1 and (about) 100 wt.% N-2, respectively. Claims 7 and 9 are dependent on claims 6 and 8, respectively, and require that the salt is at least 90 wt.% form N-1 or form N-2. The board acknowledges that the lower amount in claims 7 and 9 (90 wt.%) is in contradiction with the one implied by claims 6 and 8 (about 100 wt.%). However, a discrepancy between two claims represents a lack of clarity pursuant to Article 84 EPC rather than an insufficiency of disclosure under Article 83 EPC (see decision T 608/07, reasons, 2.5.2). Thus, the discrepancy does not lead to a lack of sufficiency of disclosure of the invention defined in claims 6 and 8 of the main request. Since the lack of clarity due to the inconsistency between claims 6 and 7 of the main request and between claims 8 and 9 of the main request was present in the granted claims, appellant 1's submission in this regard cannot succeed under Article 84 EPC either (G 3/14, OJ EPO 2015, A102, order).

3.4 Pharmaceutical composition of claim 10 of the main request

Claim 10 of the main request relates to a pharmaceutical composition comprising the cabozantinib malate salt according to any one of claims 3 to 9 and a pharmaceutically acceptable excipient.

Appellant 3 submitted that the application as filed did not contain a single example of a pharmaceutical composition comprising a cabozantinib malate salt and a pharmaceutically acceptable excipient. Furthermore, paragraph [0081] of the application as filed stated that "...*the* [pharmaceutically acceptable] *carrier should not substantially alter the form of the active compound(s)*...". This statement did not clarify the amount and the chemical nature of the pharmaceutically acceptable excipient and did not give the skilled person any guidance on carrying out the invention defined in claim 10 of the main request.

In the board's view, paragraphs [0065] and [0077] to [0086] of the application as filed provide the required information for the skilled person to prepare the pharmaceutical composition of claim 10 of the main request. Paragraph [0082] identifies suitable pharmaceutically acceptable excipients ("*sodium citrate or dicalcium phosphate or... sodium lauryl sulfate, or mixtures thereof*"). Paragraph [0082] of the application as filed refers to "*Remington's Pharmaceutical Sciences*", which represents common general knowledge in that field, for preparing the pharmaceutical compositions of claim 10 of the main request. Paragraph [0080] of the application as filed discloses how the amount of the active ingredient is to be chosen and indirectly the amount of the pharmaceutically acceptable excipient. Reference is also made in this

paragraph to "*The Pharmacological Basis of Therapeutics*", which represents common general knowledge in that field. Thus, the application as filed provides the required information that a skilled person would need to prepare the pharmaceutical composition of claim 10 of the main request.

3.5 In view of the above, the board concludes that the invention defined in the claims of the main request is sufficiently disclosed.

3.6 The respondent requested that the objections discussed in substance above under points 3.3 and 3.4 not be admitted. Since it was concluded that these objections were not convincing, there was no need to decide on the admittance of these objections.

4. Novelty - Article 54 EPC

4.1 Appellants 2 and 3 objected to the lack of novelty of the subject-matter of claim 1 in view of D29 (page 1). The main argument was that D29 implicitly disclosed the crystalline and amorphous forms of a cabozantinib malate salt and thus anticipated the crystalline form as claimed.

4.2 D29 (page 1) discloses cabozantinib (L)-malate for treatment of medullary thyroid carcinoma (a thyroid cancer). D29 only refers to the malate salt without stating whether it is crystalline. While D29 implicitly discloses that the salt is in a solid form, it cannot be deduced from D29 that the salt is crystalline. The subject-matter of claim 1 of the main request, referring to the crystalline form of a cabozantinib malate salt, is therefore not directly and unambiguously derivable from D29.

4.3 Thus, the subject-matter of claim 1 of the main request is novel in view of D29.

5. Inventive step - Article 56 EPC

5.1 Closest prior art

The appellants objected to the inventive step of the subject-matter of claim 1 in view of D29 as the closest prior art.

5.2 Distinguishing feature

As set out above, the distinguishing feature of the subject-matter of claim 1 of the main request over the disclosure of D29 is the crystalline form of the cabozantinib malate salt.

5.3 Formulation of the objective technical problem

The objective technical problem as formulated by the respondent during the oral proceedings is the provision of a cabozantinib malate salt which, as a pharmaceutical formulation, has an improved dissolution profile under physiological conditions.

The problem is solved as shown by annex 1. Annex 1 is an experimental report from the respondent on tablets and capsules comprising cabozantinib (L)-malate as the active pharmaceutical ingredient. Dissolution studies were carried out, and the percentage of drug released was measured over time.

Tables 5 and 6 of annex 1 show that when the capsules and tablets only comprise cabozantinib (L)-malate in a crystalline form (examples 1B to 6B), the percentage of released drug is higher in comparison with the same capsules or tablets comprising cabozantinib (L)-malate in a mixture of crystalline and amorphous forms (10 or

20% of amorphous form in the mixture, examples 1A to 6A). The tables thus show that if the percentage of crystalline form is increased, the percentage of released drug is higher.

This thus shows that the problem as formulated by the respondent is solved.

5.3.1 Appellant 1 submitted that the data provided in annex 1 were not a fair comparison since a composition comprising 80 wt.% of a crystalline form of cabozantinib (L)-malate and 20 wt.% of an amorphous form of cabozantinib (L)-malate could not be representative of a composition comprising 100 wt.% of an amorphous form of cabozantinib (L)-malate.

The board does not agree.

The board cannot accept the allegation that no conclusion can be drawn about the dissolution behaviour of pure crystalline versus pure amorphous cabozantinib (L)-malate. As set out above, it follows from annex 1 that a composition comprising 100% of a crystalline form performs better than a composition comprising 80% of the crystalline and 20% of an amorphous form. The only conclusion that can be reasonably drawn from this is that increasing the amount of amorphous material decreases performance. This in turn can only imply that the crystalline form as claimed must perform better than a composition comprising 100% of the amorphous form.

5.3.2 Furthermore, appellants 1, 2 and 3 submitted that the effect observed in annex 1 was affected by the co-presence of tablet/capsule excipients and the interaction of the amorphous form with the excipient. The effect depended on the amount of excipient. This was shown by, *inter alia*, examples 1A and 2A of annex

1, which contained the same proportion of amorphous form but had two different dissolution profiles.

The board cannot accept the appellants' submission.

Example 1A (table 2) is a capsule comprising 50 wt.% of cabozantinib (L)-malate and 50 wt.% of excipient. In this capsule, cabozantinib (L)-malate is a mixture of 80 wt.% of crystalline form and 20 wt.% of amorphous form.

Example 2A is a capsule comprising 31.68 wt.% of cabozantinib (L)-malate (80 wt.% crystalline and 20 wt.% amorphous) and 68.32 wt.% of excipient.

The board acknowledges that the dissolution profile shown by example 1A is different from that of example 2A. However, as submitted by the respondent, it does not change the overall conclusion that examples 1B to 6B have an improved dissolution profile compared to examples 1A to 6A, respectively, as set out above.

Since the only variable between these examples B and examples A is the presence of the amorphous form of cabozantinib (L)-malate, and not the excipients, it has been clearly shown that the effect has its origin in the distinguishing feature of claim 1 of the main request. Furthermore, the burden of proof for the allegation that an excipient effect caused by the interaction of the amorphous form with the excipient is responsible for the observation of the improved dissolution profile rests on the party making this allegation, i.e. in this case, the appellants (T 184/00, reasons, 4). In the absence of such evidence, the appellants' arguments must fail.

5.3.3 Appellant 2 submitted that the comparative examples used in annex 1 (examples 1A to 6A) fell within the scope of claim 1 of the main request since the claim did not require any limitation of the content of the crystalline form or any limitation of the level of purity.

The board does not accept appellant 2's submission. Examples 1A to 6A are the comparative examples of annex 1. They comprise a mixture of crystalline and amorphous cabozantinib (L)-malate (10 or 20 wt.%).

Claim 1 of the main request is a compound claim relating to a crystalline cabozantinib malate salt. The compound is thus restricted to a crystalline form. The claim does not use any open language and thus excludes the presence of further forms of the cabozantinib malate salt. Consequently, the comparative examples used in annex 1 do not represent compositions according to claim 1 of the main request.

This conclusion does not change even if appellant 2's argument is accepted that claim 1 covers any composition comprising some crystalline form such that it only excludes a composition with 100% of amorphous material. As set out above, and as submitted by the respondent, from annex 1 it must be concluded that the more amorphous material present in a composition, the worse its dissolution performance. Hence, any composition covered by claim 1 and still containing some crystalline form will perform better than a comparative composition containing 100% of amorphous form. Thus, even under the assumption that claim 1 covers any composition comprising some crystalline form, the effect of an improved dissolution profile can still be acknowledged.

5.3.4 Appellant 3 submitted that the amorphous form had a higher solubility than the crystalline form, as shown by D32 and D33 and expected in the art. D32 contained the comparison of the "intrinsic" dissolution rate of a 100% crystalline form and a 100% amorphous form of cabozantinib (L)-malate. The effect shown in annex 1 was an "apparent" dissolution rate depending on the presence of the excipients and the manufacturing parameters. The objective technical problem could not be formulated as submitted by the respondent.

The board does not agree.

Document D32 is a solubility test provided by appellant 3. The crystalline and amorphous forms of cabozantinib (L)-malate were separately slurried in water at 20°C. Solubility was measured after two, three and five minutes. The results show that the amorphous form has a higher solubility in water than the crystalline form.

D33 is a declaration of a technical expert, provided by appellant 3 on solubility and dissolution. The technical expert states (bottom of page 2) that the amorphous form always shows the highest solubility in specific solvents compared to crystalline forms.

However, the effect shown in annex 1 is a dissolution rate of cabozantinib (L)-malate while the effect shown in D32 relates to the solubility of cabozantinib (L)-malate. These represent two different properties as shown by D10 (last paragraph on page 5 for the dissolution rate and second last full paragraph on page 7 for the solubility). Even if the dissolution rate depends on solubility (see equation 1 on page 6 of D10), solubility is not the only factor in the dissolution rate, which also depends, *inter alia*, on

the solute molecule diffusion coefficient D, the surface area of the dissolving solid S and the diffusion layer thickness h.

Furthermore, the experiments in D32 are not carried out under the same conditions as those of annex 1. In D32, the experiments are performed in water at a pH 7 and 20°C (point 4 of D32). In contrast, the respondent's experiments of annex 1 are carried out under acidic conditions (pH 2) at 37°C, representing the conditions in the stomach and thus the physiological conditions of oral dosage.

Consequently, the results presented by D32 cannot call into question the results shown by annex 1, which are performed under physiological conditions.

5.4 Obviousness

The appellants relied on D3, D5, D7, D13, D14, D25, D26, A005 and A006 for assessing the obviousness of the solution proposed by claim 1 of the main request.

D3 (pages 208-209) and D5 (page 351, salt forms of enalapril) refer to the advantages of crystalline forms of drugs over the amorphous forms in terms of chemical and thermodynamic stability.

D7 (figure 1, page 1047), D13 (figure 1, page 29) and D25 (figure 1, page 946; page 952) give instructions for salt and crystal screening.

D14 (page 712, left column, section "Salt Selection Decision Making", fifth- and fourth-from-last lines of the first paragraph) states that "*As a practical consideration, it is essential that the NCEs* [i.e. new chemical entities] *have high purity, and that salts be*

crystallized" (text in squared brackets added by the board).

D26 (page 527, left-hand column, third paragraph; page 528, left-hand column, first paragraph) discloses that "*Polymorphs have crystal lattices which differ in the ways in which the same molecule is bound in the unit cell. The differences may reflect different ways of packing molecules in the cell, or conformational changes, which can be large. Hydrogen-bonding will be involved for most molecules of interest to the pharmaceutical industry.*" and "*In giving each development candidate the best chance of progressing, it seems better to search for polymorphs rather than to leave their appearance to time and chance with the consequent disruption.*"

A005 (page 799, left-hand column) refers to the disadvantages of amorphous pharmaceutical solids ("*It is the apparent chemical and physical instability of most amorphous pharmaceutical solids which is the major factor precluding their more widespread use in solid dosage forms.*").

A006 (page 947, left column, first full paragraph) discloses that "..., *in general the commonly held view is that amorphous materials are undesirable forms*".

The above documents only show that crystalline forms of pharmaceutical solids are preferred. However, none of the above documents includes any teaching on how to improve the dissolution profile under physiological conditions of the cabozantinib malate salt. This is not disputed by the appellants. In the absence of such a teaching, the solution provided by claim 1 of the main request is thus not obvious.

This conclusion is not in contradiction with decision T 777/08. According to this decision (headnotes), "*in the absence of any technical prejudice and in the absence of any unexpected property, the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step*". In the current case, it has been shown in annex 1 that the unexpected property of the claimed compound is an improved dissolution profile under physiological conditions. Thus, the case at hand does not correspond to the situation in case T 777/08 where no unexpected property was recognised.

5.5 Appellants 1 and 2 argued that the improved dissolution profile under physiological conditions of the crystalline form of cabozantinib (L)-malate was a mere bonus effect since the skilled person would have had ample motivation in view of the teachings of D3, D5, D7, D13, D14, D25, D26, A005 and A006 to select the crystalline form of cabozantinib (L)-malate, the compound disclosed in D29.

The board does not agree.

A "bonus effect" arises when the state of the art forces the skilled person to adopt a certain solution, the lack of alternatives leading to a "one-way street" situation. In such a situation, any additional effect does not necessarily contribute to inventive step (see e.g. T 405/17, reasons, 4.3.3). However, this situation does not apply in this case for the following reasons.

Even if, as set out above, the passages of the documents relied on by the appellants disclose that a crystalline form is preferred, this is not the only teaching available in these documents and the art, as submitted by the respondent. D3 (page 208, left column,

last paragraph) teaches that "*amorphous solids are occasionally preferred because they undergo dissolution at a faster rate*". The same teaching is found in D25, which discloses that the amorphous forms may be of interest (page 946, left column, last paragraph; page 952, left column "Amorphous forms") since these forms "*usually are much more soluble than their crystalline counterparts*". D13 (page 50) does not exclude the amorphous calcium salt of L-649,923 in the process of salt screening and selection to improve stability. A005 (introduction on page 799) refers to the "*use of amorphous form of drugs to improve solubility, increase dissolution and promote therapeutic activity*". A006 (abstract on page 946) teaches that amorphous solids and crystalline salts are both of interest as a means of improving the dissolution characteristics and apparent solubility of poorly water-soluble active pharmaceutical ingredients which have low bioavailability in humans. D35 (page 216, first paragraph of "Discussion") discloses that "*Usually the dissolution rate of a compound increases when converted into its amorphous state*".

In view of the above disclosures and teachings, there is no indication in the prior art that in searching for an adequate solid form of the compound disclosed in the closest prior-art document D29, the skilled person would have been forced specifically to choose only the crystalline form of cabozantinib (L)-malate as required by claim 1 of the main request. Thus, the improved dissolution profile under physiological conditions of the crystalline form of cabozantinib (L)-malate, as shown in annex 1, cannot be considered a mere bonus effect.

5.6 Appellant 1 further submitted that the case at hand was an obvious-to-try situation since the claimed subject-matter was the result of a selection of one component, i.e. the crystalline form, from a list of two alternatives, namely the crystalline and amorphous forms. The prior art taught to select the crystalline form.

The board does not agree. In the problem-solution approach, the question to be answered is whether the skilled person, having regard to the closest prior art and being faced with the objective technical problem, would have been motivated by the prior art to arrive at the claimed solution or would have had at least a reasonable expectation that a suggested investigation would be successful. In such a case, inventive step can be denied (T 1684/16, reasons, 4.3.4). However, in the case at hand, the skilled person would not have arrived at the subject-matter of claim 1 of the main request because no such motivation or suggestion is available in the documents relied on by the appellants (see 5.4 above) that a crystalline form of a cabozantinib malate salt has an improved dissolution profile under physiological conditions in a pharmaceutical formulation.

6. Admittance of the submissions based on plausibility

6.1 With the statement of grounds of appeal, appellant 2 submitted that it was not made plausible on the basis of the content of the application as filed that the claimed compounds achieved the effect shown in annex 1, namely the improved dissolution profile. Therefore, the post-published data of annex 1 were not to be taken into consideration in the formulation of the objective

technical problem. This objection is referred to below as the "plausibility objection".

The respondent requested with the letter of 20 October 2020 that this objection not be admitted.

During the oral proceedings, appellants 2 and 3 requested that the respondent's request for non-admittance of appellant 2's submissions on a lack of plausibility not be admitted into the proceedings.

6.2 Admittance of respondent's request for non-admittance of appellant 2's plausibility objection

As set out above, the respondent's request for non-admittance of appellant 2's plausibility objection was submitted with the letter of 20 October 2020, i.e. after the first summons to oral proceedings. Since the first summons to attend oral proceedings was notified before the date of the entry into force of the revised version of the RPBA on 1 January 2020, Article 13(2) RPBA 2020 does not apply and Article 13 RPBA 2007 continues to apply (T 1083/16, reasons, 2.1 to 2.2).

In exercising its discretion under Article 13(1) and (3) RPBA 2007, the board considers, *inter alia*, the state of the proceedings, the complexity of the new subject-matter submitted, and the need for procedural economy (Article 13(1) RPBA 2007). Furthermore, amendments of a party's case made after oral proceedings have been arranged are not admitted if they raise issues which the board or the other party cannot reasonably be expected to deal with without adjournment of the oral proceedings (Article 13(3) RPBA 2007).

The board decided to admit the respondent's request into the proceedings for the following reasons.

The respondent's request focuses on procedural issues, namely whether appellant 2's plausibility objection should be admitted into the appeal proceedings. The main point to be examined as regards the respondent's objection is whether appellant 2's plausibility objection could and should have been filed in the opposition proceedings (see below). This did not raise any complex new issue, and the admittance of the respondent's request did not lead to a fresh case to be considered at an extremely late stage of the appeal proceedings. This was not disputed by the appellants. The admittance of the respondent's request was also not detrimental to procedural economy (Article 13(1) RPBA 2007) and it could be dealt with without adjournment of the oral proceedings (Article 13(3) RPBA 2007).

6.3 Admittance of appellant 2's plausibility objection

As set out above, appellant 2's plausibility objection was raised in the statement of grounds of appeal. Consequently, the admittance of the objection is governed by Article 12(4) RPBA 2007 (see the transitional provisions pursuant to Article 25(2) RPBA 2020, the statement of grounds of appeal having been filed before 1 January 2020).

In the proceedings before the opposition division, the parties had discussed the data presented in annex 1 as to their merits, i.e. the parties had proceeded on the basis that the data could be taken into account and the decision under appeal is based thereupon. Hence, as not disputed by the parties, the objection of lack of plausibility and whether the post-published data in annex 1 were to be taken into account had not been

discussed in the proceedings before the opposition division.

Furthermore, appellant 2 did not argue that the objection was submitted in response to facts, objections, arguments or evidence presented at a late stage of proceedings before the opposition division, and on which the decision under appeal was based, and the board saw no reason that justified the submission of the objection only at the appeal stage.

It is the primary object of the appeal proceedings to review the decision under appeal in a judicial manner, as now explicitly confirmed in Article 12(2) RPBA 2020. Admitting the objection into the proceedings would have given appellant 2 a new chance, after opposition proceedings which had been instituted by it and having been terminated, to object to inventive step based on an entirely new submission. The admittance of the plausibility objection would have led to an entirely fresh case regarding inventive step. More specifically, had the plausibility objection been admitted and found convincing, the post-published data in annex 1 would have had to be disregarded, and the effect relied upon by the respondent could not have been taken into account. The objective technical problem would thus have changed, and the obviousness as regards a different objective technical problem would have had to be considered for the first time during the appeal proceedings.

In light of the above, the objection not only could but also should have been presented during the proceedings before the opposition division. Accordingly, the board decided not to admit the plausibility objection in

accordance with Article 12(4) RPBA 2007 and Article 12(2) RPBA 2020.

6.4 Appellant 2 argued that the submissions on plausibility did not constitute an allegation of fact but rather an argument and that the board did not have any discretion not to admit an argument.

The board does not agree. The appellant's allegation was that the application as filed did not make it plausible that the claimed subject-matter resulted in an improved dissolution profile. Whether, on the basis of the application as filed, it can be concluded that a certain effect, here an improved dissolution profile, is plausible or not is based on a factual consideration rather than a mere argument. More specifically, numerous facts play a role in making this consideration, such as what is actually disclosed in the application as filed as regards the effect and what the technical relationship between the claimed compound and the effect is. Therefore, appellant 2's submissions on plausibility included an allegation of fact (see also T 1875/15, reasons, 2.3 to 2.4), and the board had under Article 114(2) EPC the discretion not to admit appellant 2's late-filed submissions.

6.5 Appellant 2 also argued that the plausibility objection could only be raised with the statement of grounds of appeal since the case law on plausibility cases involving "small" molecules, such as the one defined in claim 1, was only developed after the proceedings before the opposition division. Reference was made to decisions T 415/11 (reasons, 50, 12 January 2012), T 1329/04 (reasons, 12, 28 June 2005), T 488/16 (reasons, 4.2, 1 February 2017) and T 184/16 (reasons, 2.1 to 2.8, 7.2 and 11, 12 December 2019).

The board does not agree. Appellant 2's notice of opposition was filed on 5 December 2013. Oral proceedings before the opposition division took place on 14 December 2015. The board acknowledges that T 1329/04 (reasons, 12) relates to the plausibility issue in a case concerning polynucleotides, which might be considered what appellant 2 terms "large" molecules. While it can be accepted that other decisions such as T 488/16 (of 1 February 2017) or T 184/16 (of 12 December 2019) on the plausibility of "small" molecules were issued after the proceedings before the opposition division, the board observes that other decisions such as T 710/05 (glutathione, a C_{10} molecule; of 22 February 2007) relate to the plausibility of "small" molecules and thus the concept of plausibility of "small" molecules was known in the case law on the date when the opposition was filed. Furthermore, the board does not see, and appellant 2 has not brought forward any argument, why the case law on "large" molecules should be different from that on "small" molecules and thus why appellant 2 should not have taken into account the case law on "large" molecules, such as T 1329/04, which was available before the opposition was filed. Thus, appellant 2's submission is not convincing.

7. Admittance of the submissions relating to a bonus effect

7.1 As set out above (see 5.7 above), appellants 1 and 2 submitted that the results in annex 1 (improved dissolution profile) were to be considered only a bonus effect.

7.2 The respondent requested that the submissions relating to a bonus effect, being associated with new

allegations of fact, not be admitted into the proceedings.

During the oral proceedings, appellants 2 and 3 requested that the respondent's request for non-admittance of appellants 1 and 2's submissions relating to a bonus effect should not be admitted into the proceedings.

7.3 Admittance of the respondent's request for non-admittance of appellants 1 and 2's submissions relating to a bonus effect

During the oral proceedings, the board rejected the respondent's request and admitted the submissions of appellants 1 and 2 based on the bonus effect into the proceedings, pursuant to Article 12(4) RPBA 2007.

There was therefore no need to decide on appellants 2 and 3's objection not to admit into the proceedings the respondent's objection not to admit the appellants' submissions relating to a bonus effect.

7.4 Admittance of appellants 1 and 2's submissions relating to a bonus effect

During the oral proceedings, as set out above, the board rejected the respondent's request and admitted the submissions of appellants 1 and 2 relating to a bonus effect into the proceedings, pursuant to Article 12(4) RPBA 2007.

Although these submissions were admitted, the board still found that the claims of the main request involved an inventive step (see point 5.4 above). Thus, a detailed reasoning on the rejection of the respondent's request not to admit into the proceedings

appellant 1 and 2's submissions relating to a bonus effect does not need to be given.

8. Admittance of the submissions on the particle size used in annex 1 and the use of film-coated tablets

8.1 During the oral proceedings, appellant 3 submitted that the effect shown in annex 1 depended on the particle size of cabozantinib (L)-malate. The particle size of this compound played a role in its dissolution. Since there was no indication of the particle size of the different forms of cabozantinib (L)-malate tested, the results of annex 1 were not conclusive.

Appellant 2 submitted during the oral proceedings that the tablets used in annex 1 were film-coated tablets, with the film interacting with the dissolution of the active ingredient. In the absence of clear information on the preparation and formulation of the film of the tablet, the results shown by annex 1 could not be taken into consideration.

8.2 The respondent requested that the above submissions not be admitted into the proceedings.

8.3 The above submissions were made for the first time during the oral proceedings before the board. They thus represented an amendment to appellants 1 and 3's cases. As set out above, Article 13 RPBA 2007 applies in this appeal case for any amendment to a party's case after the summons to oral proceedings.

In the case at hand, the submissions on the particle size used in annex 1 and the use of film-coated tablets were made at the latest possible stage of the appeal proceedings, namely at the oral proceedings. The submissions were an attempt to make the board disregard the effect shown by the data contained in annex 1 for

the formulation of the objective technical problem. The submissions raised new factual issues on technical matters, namely the relationship between the particle size and the solubility and the relationship between the nature of a film on a tablet and the solubility, which would have had to be addressed by the parties and considered by the board for the first time at the oral proceedings. The respondent could not have been reasonably expected to be able to deal with such new issues without further preparation. The admittance of the submissions would have been contrary to procedural economy.

8.4 In light of the above considerations, the board decided not to admit the submissions on the particle size used in annex 1 and the use of film-coated tablets into the proceedings pursuant to Article 13(1) and (3) RPBA 2007.

9. Appellant 1 requested that A001 to A005 be admitted into the proceedings. Appellant 3 requested that A006 be admitted into the proceedings.

A001 to A006 were filed with a the statement of grounds of appeal and, hence, their admittance into the proceedings was to be considered under Article 12(4) RPBA 2007. Considering the circumstances of the present case, the board saw no reason to exclude these documents from the appeal proceedings, also in view of the fact that there was no request by the respondent to this effect.

A004 to A006 were considered in substance in the context of the objection of lack of sufficiency and the objection of lack of inventive step (see points 3.2, 5.4 and 5.5 above).

A001 is a book extract defining the terms "solubility" and "dissolution". A002 and A003 are IUPAC definitions of said terms. These documents were not relevant to the outcome of the present decision.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated